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Pre-admission glucagon-like peptide-1 receptor agonist (GLP-1RA) and mortality from coronavirus disease 2019 (Covid-19): A systematic review, meta-analysis, and meta-regression

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ABSTRACT

Aims: GLP-1RA has many beneficial properties, including anti-inflammatory, anti-obesogenic, pulmonary protective effects as well as beneficial impact on gut microbiome. However, the evidence regarding the benefit of GLP-1RA in Covid-19 patients with diabetes is still unclear. This study sought to analyze the benefit of pre-admission use of GLP-1RA in altering the mortality outcomes of coronavirus disease 2019 (Covid-19) patients with diabetes mellitus.

Methods: Using specific keywords, we comprehensively searched the potential articles on PubMed, Europe PMC, and medRxiv database until June 12th, 2021. All published studies on Covid-19 and GLP-1RA were retrieved. Statistical analysis was conducted using Review Manager 5.4 and Comprehensive Meta-Analysis version 3 software.

Results: A total of 9 studies with 19,660 diabetes mellitus patients who were infected by SARS-CoV-2 were included in the meta-analysis. Our data suggested that pre-admission use of GLP-1RA was associated with reduction in mortality rate from Covid-19 in patients with diabetes mellitus (OR 0.53; 95 %CI: 0.43–0.66, $p < 0.00001$, $I^2 = 0\%$, random-effect modelling). Further analysis showed that the associations were not influenced by age ($p = 0.213$), gender (p = 0.421), hypertension (p = 0.131), cardiovascular disease (p = 0.293), nor the use of metformin (p = 0.189) and insulin (p = 0.117).

Conclusions: Our study suggests that pre-admission use of GLP-1RA may offer beneficial effects on Covid-19 mortality in patients with diabetes mellitus. However, more randomized clinical trials are required to confirm this conclusion.

1. Introduction

The emergence of Covid-19 disease since the first case on December 2019 had caused up to 177,108,695 confirmed cases, including 3,840,223 deaths per June 2021 according to WHO.[1] Cases' severity varied among all age populations depending on their comorbidities. Diabetes mellitus and obesity were found to be two of important risk factors which may

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contribute to the development of severe form of Covid-19, causing further inflammation and immune dysfunction that leads to the formation of cytokines storm which is life threatening.[2-7] Several therapies had been proposed to control and manage these conditions.[8-14] Recently the use of GLP1-RA, as one alternative to treat DM patients, had shown promising effect to reduce excessive inflammation-induced acute lung injury and improving Covid-19 outcome.[15] In addition to stimulating postprandial insulin secretion, GLP1-RA also seems to have beneficial properties such anti-inflammatory, anti-obesogenic, pulmonary protective effects and gut microbiome modulating effects.[16] Furthermore, an experimental study on rats showed that the use of GLP1-RA (liraglutide) was capable to stimulate pulmonary ACE2 expression, an enzyme that has been demonstrated to oppose the pathway that is responsible for the progression of acute respiratory distress syndrome (ARDS), including the one caused by SARS-CoV-2 infection.[17,18] However, the evidences regarding benefit of GLP-1RA in Covid-19 patients are still unclear. Therefore, the objective of this study is to evaluate and analyze the association between GLP1-RA and Covid-19 mortality.

2. Materials and methods

2.1. *Eligibility criteria*

The protocol of this study was registered in PROSPERO (CRD42021260638). The articles analyzed in this study has qualified the following entry criteria: fulfill the PICO framework (P: patients with diabetes mellitus who were infected with SARS-CoV-2; I: pre-admission use of GLP-1RA; C: the use of any other anti-diabetic drugs besides GLP-1RA prior to admission into the hospital; O: mortality from Covid-19), cohort, case-control, cross-sectional, and randomized or non-randomized clinical trial studies were included. All studies aside from original research articles (review articles, letter to editor or correspondence), case-series or case report studies, studies presented in any other language besides English, articles focusing on people below 18 years of age and pregnant women were excluded.

2.2. *Search strategy and study selection*

The articles from three databases (PubMed, Europe PMC, and medRxiv) were searched systemically. Search terms used include “GLP-1” OR “GLP-1RA” OR “glucagon-like peptide-1” OR “dulaglutide” OR “semaglutide” OR “exenatide” OR “liraglutide” AND “diabetes” OR “diabetes mellitus” AND “SARS-CoV-2”, OR “coronavirus disease 2019” OR “Covid-19” in a time range from 2019 until June 12, 2021 with English-language restriction. Our searching strategy details are listed in Table 1. Initial screening of titles and abstracts was conducted to identify eligible articles. Searches of potential articles were also done by analyzing the list of references of eligible studies. The strategy for searching the article was presented in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram.

2.3. *Data extraction and quality assessment*

Two researchers (TIH, DI) performed the data extraction. Every essential information about the study, including the characteristic of the population (age, gender, hypertension, cardiovascular disease, metformin and insulin usage/consumption), the number of patients who use GLP-1RA, as well as the mortality in Covid-19 patients were listed and arranged in one form.

Table 1 – Literature search strategy.

Database	Keyword	Result
PubMed	(“glucagon-like peptide 1”[MeSH Terms] OR ”glucagon-like peptide 1”[All Fields] OR “glp 1”[All Fields]) OR GLP-1RA[All Fields] OR (”dulaglutide“[Supplementary Concept] OR ”dulaglutide“[All Fields]) OR (”semaglutide“[Supplementary Concept] OR ”semaglutide“[All Fields]) OR (”exenatide“[MeSH Terms] OR ”exenatide“[All Fields]) OR (”liraglutide“[MeSH Terms] OR ”liraglutide“[All Fields]) AND (”diabetes mellitus“[MeSH Terms] OR (”diabetes“[All Fields] AND ”mellitus“[All Fields]) OR ”diabetes mellitus“[All Fields] OR ”diabetes“[All Fields] OR ”diabetes insipidus“[MeSH Terms] OR (”diabetes“[All Fields] AND ”insipidus“[All Fields]) OR ”diabetes insipidus“[All Fields]) AND (”COVID-19”[All Fields] OR “COVID-19”[MeSH Terms] OR ”COVID-19 Vaccines“[All Fields] OR ”COVID-19 Vaccines“[MeSH Terms] OR ”COVID-19 serotherapy“[All Fields] OR ”COVID-19 Nucleic Acid Testing“[All Fields] OR ”covid-19 nucleic acid testing“[MeSH Terms] OR ”COVID-19 Serological Testing“[All Fields] OR ”covid-19 serological testing“[MeSH Terms] OR ”COVID-19 Testing“[All Fields] OR ”covid-19 testing“[MeSH Terms] OR ”SARS-CoV-2”[All Fields] OR “sars-cov-2”[MeSH Terms] OR ”Severe Acute Respiratory Syndrome Coronavirus 2”[All Fields] OR “NCOV”[All Fields] OR “2019 NCOV”[All Fields] OR ((“coronavirus”[MeSH Terms] OR “coronavirus”[All Fields] OR “COV”[All Fields]) AND 2019/11/01[PubDate]: 3000/12/31[PubDate]))	25
Europe PMC	“GLP-1” OR “GLP-1RA” OR “glucagon-like peptide-1” OR “dulaglutide” OR “semaglutide” OR “exenatide” OR “liraglutide” AND “diabetes” OR “diabetes mellitus” AND “SARS-CoV-2”, OR “coronavirus disease 2019” OR “COVID-19”	156
medRxiv	“GLP-1” OR “GLP-1RA” OR “glucagon-like peptide-1” OR “dulaglutide” OR “semaglutide” OR “exenatide” OR “liraglutide” AND “diabetes” OR “diabetes mellitus” AND “SARS-CoV-2”, OR “coronavirus disease 2019” OR “COVID-19”	19

Mortality from COVID-19, defined by the total number of patients who died during the follow-up period with positive Covid-19 status, will be the outcome of interest.

Two researchers (JEH, CP) assessed the quality of each study included in this study independently. The case-control and cohort studies' quality were evaluated by using Newcastle–Ottawa Scale (NOS). The assessment reviews the selection, comparability, and outcome of each study, then each study was assigned a total score from zero to nine. A score of ≥7 is considered a good quality study.[19]

2.4. *Statistical analysis*

Review Manager 5.4 (Cochrane Collaboration) software and Comprehensive Meta-Analysis version 3 were used to perform the meta-analysis and meta-regression. Generic-Inverse Variance formula was utilized to calculate the odds ratio (OR) and its 95% confidence interval (95 %CI) for the mortality outcome. The heterogeneity was assessed by using the I^2 statistic with a value of <25%, 26–50%, and >50% were considered as low, moderate, and high degrees of heterogeneity, respectively. Meta-regression with random-effects model was performed using a restricted-maximum likelihood for pre-specified variables including age, gender, hypertension, cardiovascular disease, and the use of metformin. Funnel plot analysis was used to evaluate the qualitative risk of publication bias, while the quantitative risk was assessed by using the Egger's regression method.[20]

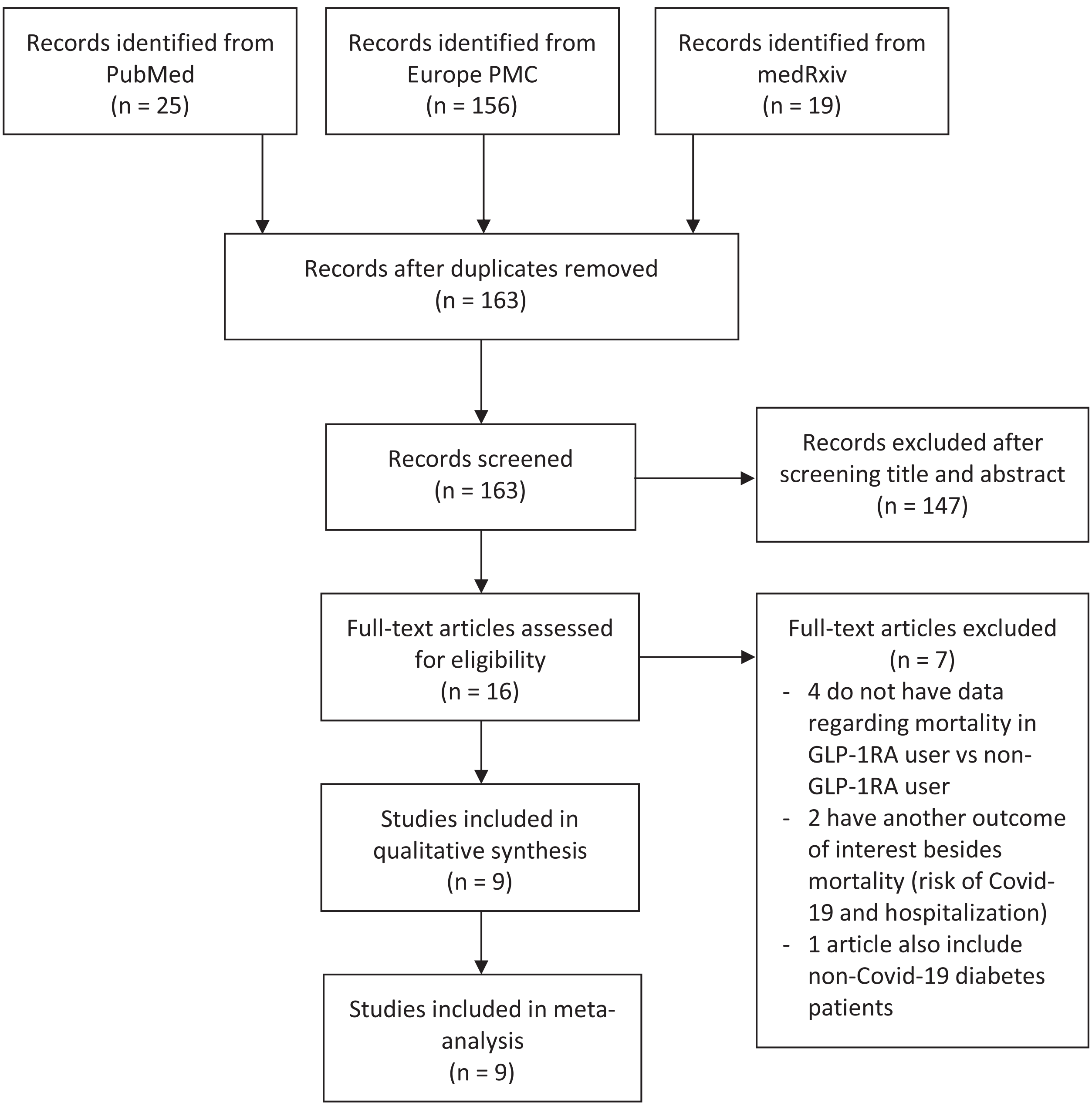

Fig. 1 – PRISMA diagram of the detailed process of selection of studies for inclusion in the systematic review and meta-analysis.

Table 2 – Characteristics of included studies.

Study	Sample size	Design	Country	Overall age mean ± SD	Male n (%)	Hypertension n (%)	Cardiovascular disease n (%)	Metformin use n (%)	Insulin use	GLP-1RA use n (%)	
										Death	Alive
Cariou B et al. [21] 2020	1317	Retrospective cohort	France	69.8 ± 13	855 (64.9%)	1003 (77.2%)	621 (47.1%)	746 (56.6%)	504 (38.3%)	9 (6.4%)	114 (9.7%)
Israelsen SB et al.[22] 2021	996	Retrospective cohort	Denmark	60 ± 14	521 (52.3%)	N/A	N/A	645 (64.7%)	224 (24.8%)	14 (26.4%)	356 (42%)
Izzi-Engbeaya C et al.[23] 2021	337	Retrospective cohort	England	65.8 ± 17.5	202 (60%)	238 (70.6%)	91 (27%)	169 (50.1%)	108 (31%)	No data on death/alive Total = 5 (1.4%)	
Nyland JE et al.[24] 2020	12,954	Retrospective cohort	USA	62.2 ± 15.2	6244 (48.2%)	5881 (45.4%)	3420 (26.4%)	6192 (47.8%)	7435 (57.4%)	32 (2.9%)	797 (6.7%)
Orioli L et al. [25] 2021	73	Retrospective cohort	Belgium	69 ± 14	35 (48%)	59 (80.8%)	32 (43.8%)	45 (61.6%)	31 (45.6%)	0 (0%)	5 (8.8%)
Ramos-Rincon JM et al.[26] 2021	790	Retrospective cohort	Spain	85.8 ± 4.5	418 (52.9%)	666 (84.3%)	625 (79.1%)	420 (53.1%)	211 (26.7%)	11 (2.9%)	13 (3.3%)
Silverii GA et al.[27] 2021	159	Retrospective cohort	Italy	73.3 ± 12.6	86 (54.1%)	N/A	N/A	76 (47.8%)	43 (27%)	1 (1.7%)	6 (6%)
Sourij H et al. [28] 2020	238	Retrospective cohort	Austria	71.1 ± 12.9	152 (63.9%)	169 (71%)	160 (67.2%)	77 (32.3%)	52 (21.9%)	0 (0%)	3 (1.7%)
Wargny M et al.[29] 2021	2796	Retrospective cohort	France	69.7 ± 13.2	1782 (63.7%)	2126 (76.8%)	302 (11.4%)	1553 (55.6%)	1039 (37.2%)	33 (5.7%)	221 (10%)

3. Results

3.1. Study selection and characteristics

The searches on the databases yielded 195 studies. Through eliminating duplicates articles, a total of 163 records remained to be further assessed. Another 147 studies were removed after screening through the titles and abstracts while matching the inclusion and exclusion criteria. Further evaluation for its eligibility on the remaining 16 full-text articles was completed. A total of 7 articles were excluded in which four articles had no data regarding the mortality in GLP-1RA user compared with non GLP-1RA user, another two have another outcome of interest besides mortality (risk of Covid-19 and hospitalization), and lastly one article also include non-Covid-19 diabetes patients. The details regarding excluded articles can be seen in Appendix A. As a result, 9 studies were included in this meta-analysis[21-29] with an overall of 19,660 Covid-19 patients with diabetes mellitus (Fig. 1). All 9 studies were retrospective cohort studies, and the characteristics of each studies were shown in Table 2.

3.2. Quality of study assessment

Quality assessment of cohort and case-control studies using NOS scale indicated all included studies had a good quality (Table 3). Altogether, all studies were acceptable to be further analyzed using meta-analysis.

3.3. GLP-1RA and mortality outcome

Our pooled analysis showed that pre-admission use of GLP-1RA in diabetes mellitus patients was associated with reduction of mortality rate from Covid-19, with no relevant heterogeneity (OR 0.53; 95 %CI: 0.43–0.66, $p < 0.00001$, $I^2 = 0\%$, random-effect modelling) (Fig. 2).

3.4. Meta regression

Our meta-regression suggested the association between pre-admission use of GLP-1RA and mortality from Covid-19 was not affected by age (p = 0.213) (Fig. 3A), gender (p = 0.421) (Fig. 3B), hypertension (p = 0.131) (Fig. 3C), cardiovascular disease (p = 0.293) (Fig. 3D), nor the use of metformin (p = 0.189) (Fig. 3E) and the use of insulin (p = 0.117) (Fig. 3F).

3.5. Publication bias

Funnel plot analysis showed a relatively symmetrical inverted-plot (Fig. 4), while Egger's regression method also showed non-significant result (p = 0.737) for the association between pre-admission GLP-1RA use and mortality outcome, showing no indication of publication bias.

4. Discussion

Our analysis shows that pre-admission use of GLP-1RA is associated with reduced mortality in COVID-19 patients with

Table 3 – Newcastle-Ottawa quality assessment of observational studies.

First author, year	Study design	Selection	Comparability	Outcome	Total score	Result
Cariou B et al.[21] 2020	Cohort	***	**	***	8	Good
Israelsen SB et al.[22] 2021	Cohort	***	**	**	7	Good
Izzi-Engbeaya C et al.[23] 2021	Cohort	***	**	***	8	Good
Nyland JE et al.[24] 2020	Cohort	**	**	***	7	Good
Orioli L et al.[25] 2021	Cohort	***	**	***	8	Good
Ramos-Rincon JM et al.[26] 2021	Cohort	***	**	***	8	Good
Silverii GA et al.[27] 2021	Cohort	**	**	***	7	Good
Sourij H et al.[28] 2020	Cohort	***	**	***	8	Good
Wargny M et al.[29] 2021	Cohort	***	**	***	8	Good

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Cariou B et al. 2020	−0.4453	0.3584	9.3%	0.64 [0.32, 1.29]
Israelsen SB et al. 2021	−0.4338	0.3119	12.3%	0.65 [0.35, 1.19]
Izzi–Engbeaya C et al. 2021	−0.6539	0.8949	1.5%	0.52 [0.09, 3.00]
Nyland JE et al. 2020	−0.8435	0.1832	35.7%	0.43 [0.30, 0.62]
Orioli L et al. 2021	−0.7885	1.512	0.5%	0.45 [0.02, 8.80]
Ramos–Rincon JM et al. 2021	−0.12	0.416	6.9%	0.89 [0.39, 2.00]
Silverii GA et al. 2020	−1.3089	1.093	1.0%	0.27 [0.03, 2.30]
Sourij H et al. 2021	−0.836	1.5194	0.5%	0.43 [0.02, 8.52]
Wargny M et al. 2021	−0.6007	0.1928	32.2%	0.55 [0.38, 0.80]
Total (95% CI)			**100.0%**	**0.53 [0.43, 0.66]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.96$, df = 8 (P = 0.86); $I^2 = 0\%$
Test for overall effect: Z = 5.75 (P < 0.00001)

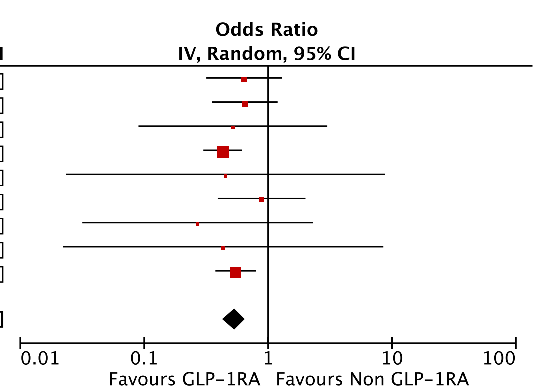

Fig. 2 – Forest plot that demonstrates the association of pre-admission GLP-1RA use with mortality outcome.

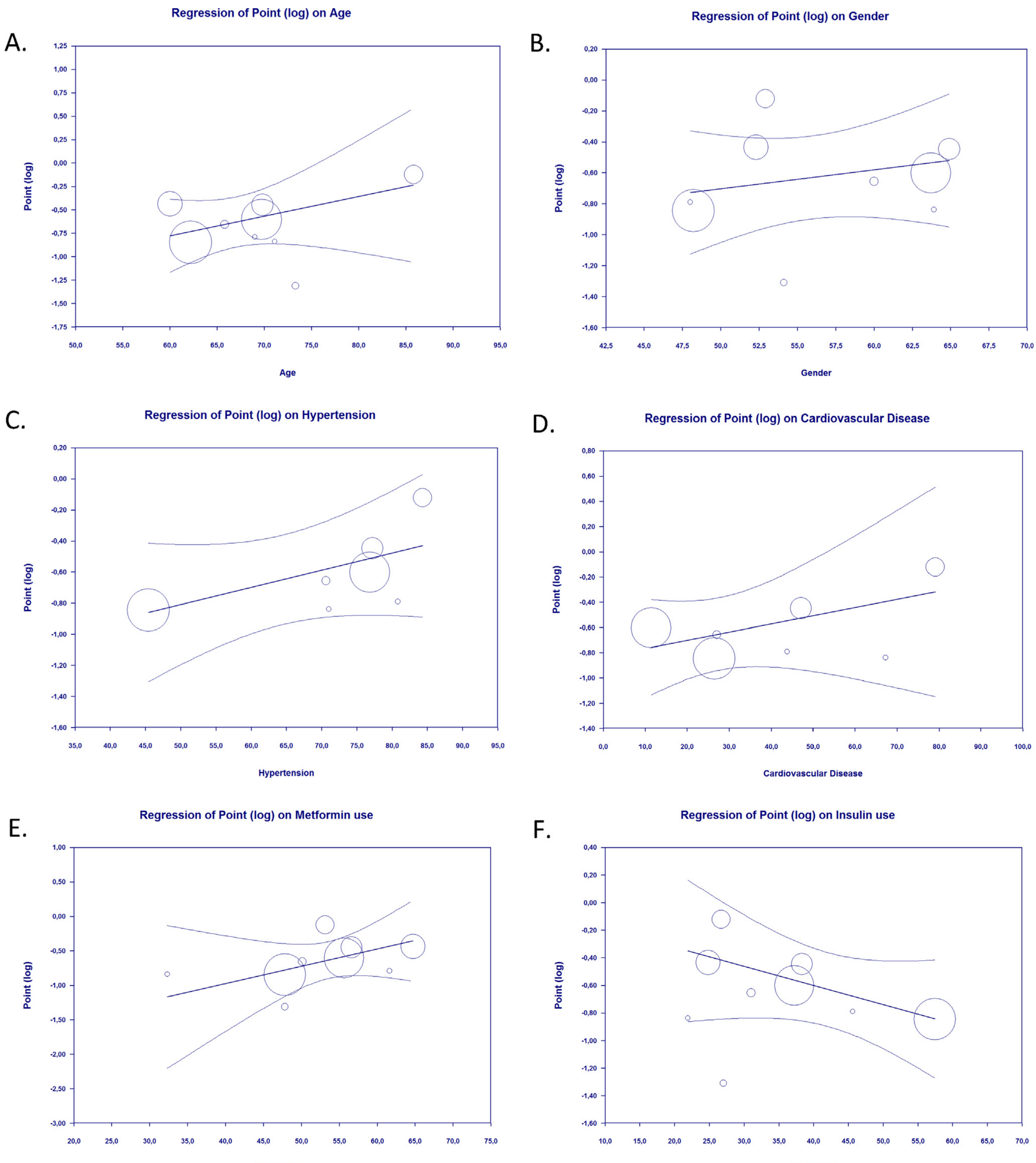

Fig. 3 – Bubble-plot for Meta-regression. Meta-regression analysis showed that the association between pre-admission GLP-1RA use and mortality outcome was not affected by age (A), gender (B), hypertension (C), cardiovascular disease (D), the use of metformin (E), and the use of insulin (F).

diabetes mellitus. This association was not affected by age, gender, hypertension, cardiovascular disease, nor the use of metformin and insulin.

There are some explanations how GLP-1RA could affect the prognosis of Covid-19 patients. Glucagon-like peptide-1 (GLP-1), an incretin hormone, is responsible for facilitating postprandial insulin secretion. GLP-1-based drugs work on GLP-1 receptors (GLP-1R) that are primarily located on epithelial of the lung and immune cells. In COVID-19 patients, with or without DM, GLP-1RA have been considered to have several

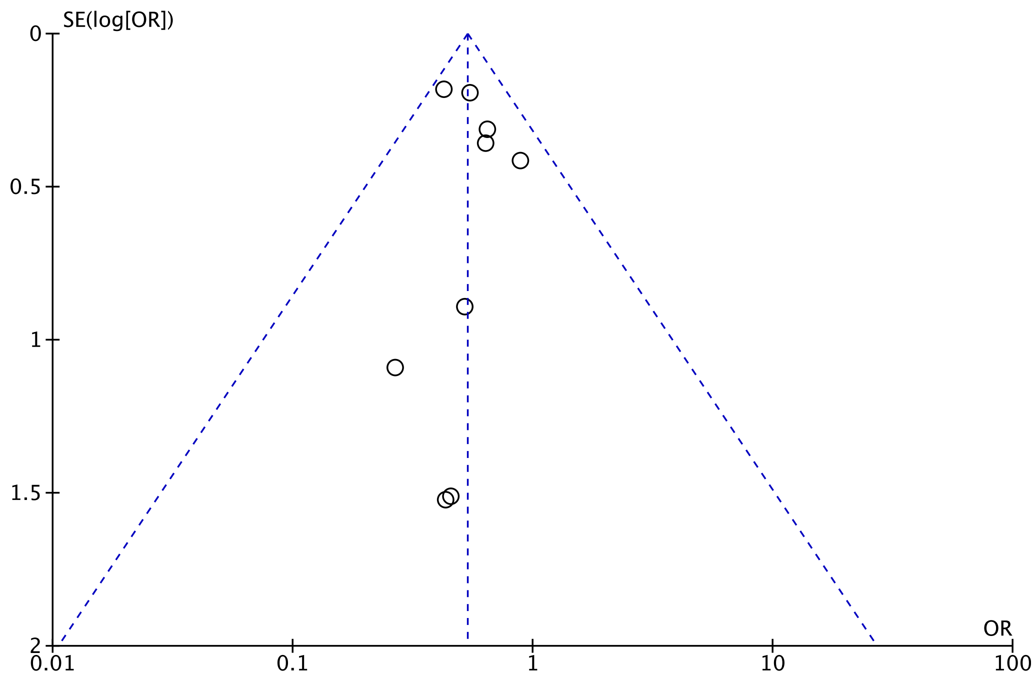

Fig. 4 – Funnel plot analysis for the association of pre-admission GLP-1RA use with mortality outcome.

mechanisms that may improve the outcome of the disease. Besides their glucose-lowering effects, they serve multiple benefits on controlling lung injury caused by inflammation through pulmonary protective effects, anti-obesogenic properties, and modulation of gut microbiota.[30]

Frequent fluctuations of uncontrolled blood glucose level may build up oxidative stress, causing further production of inflammatory cytokines and dysregulation of the innate and adaptive immunity.[31] Furthermore, there has been a speculation that SARS-CoV-2 viral replication will be promoted in the state of elevated glucose levels.[32,33] Therefore, controlling blood glucose level is important as part of treatment strategy in COVID-19 patients. GLP1-RA is an excellent agent for non-severe COVID-19 (Insulin is still the treatment of choice for severe COVID-19 with type 2 Diabetes) because it has high efficacy in controlling blood glucose level with low risk of hypoglycemia[30] and there is no considerable disadvantage of GLP-1RA that may interfere metabolism in COVID-19 patients with diabetes.[34]

Minor concern regarding GLP-1RA effects on promoting the expression of angiotensin converting enzyme-2 (ACE-2) has also been proposed. To enter pulmonary epithelial cells, SARS-CoV2 attaches to ACE-2 receptors, hence any drug that upregulates the receptor may worsen the outcome of the infection. GLP-1RA may stimulate ACE2 expression, although it still remains unknown whether the drugs increase ACE2 expression in human population.[35,36]

In addition to pancreas, GLP-1-based drugs show anti-inflammatory and immunoregulatory effect in multiple organs. GLP-1R is abundantly expressed in multiple organs including brain, pancreas, kidney, stomach, heart, and predominantly in lung epithelia and immune cells.[37] GLP-1RA mainly express its anti-inflammatory properties through the suppression of cytokine and chemokine production, stimulation of eNOS/sGC/PKG signaling pathway, inactivation of the NF-B signaling, as well as attenuation of thioredoxin-interacting protein levels.[35] Animal studies in mice with experimental lung injury also showed that GLP-1RA reduce mucus secretion, and preserve lung function.[38-42] In addition, Rogliani et al.[43] reported that GLP-1RAs improves forced expiratory volume in 1 s - FEV1, forced vital capacity - FVC, and maximal expiratory flow at 75% and 50% - MEF75 and MEF50 in diabetes mellitus patients, regardless on their blood glucose levels.

GLP-1R expressed copiously in lungs. In an animal study conducted at rats, GLP-1 improved pulmonary physiology and surfactant production.[18] GLP-1 owns anti-inflammatory and anti-atherogenic properties. Several inflammatory markers and cardiovascular markers (e.g. C-reactive protein) are reduced in Type 2 diabetes patients treated with GLP-1RA.[44] GLP-1 inhibited IL-1β production, cytokine secretion, interfere nuclear factor-kB pathway, and promoted survival after lipopolysaccharide induced systemic inflammation in rats. The fact that GLP-1 displays anti-inflammatory effects and GLP-1R presence in the lung further support that GLP-1RA might attenuate acute lung disease.[37,38,45,46]

GLP-1RA also seem to affect the activity of neural pathways involved in food intake, reward, and energy expenditure and thus have the ability to decrease body weight.[47] Long-acting GLP-1RA usage consistently results in significant weight loss.[48-50] Furthermore, liraglutide is also used for treating obesity/overweight patients with hypertension, diabetes, and dyslipidemia as a supporting drug to diet and exercise due to clinically significant weight loss, reduction in blood glucose level variability and multiple cardiometabolic risk factors. Weight reduction properties of GLP-1RA is favorable in overweight/obese COVID-19 patients because high BMI is associated with multiple drawbacks that increase susceptibility to COVID-19 such as chronic inflammation, high ACE-2 expression, and decreased vitamin D level, thus, decreasing fat mass opposes those risk factors.[48-50]

In an animal study GLP1-RA seems to be capable of reversing gut microbiota dysbiosis (Low Bacteroidetes/Firmicutes ratio) caused by type 2 diabetes mellitus/obesity. It is proposed that GLP-1 modulates gut microbiota by delaying gastric emptying time and gut transit time (thus affecting intraluminal environment), binding to neurons within hypothalamus (interfering gut-brain axis), and modulating appetite, weight loss, and glucose homeostasis.[51] Since dysbiosis causes increased intestinal permeability, endotoxemia, and activation of NF-B and other inflammatory pathways, any infectious diseases including COVID-19 might progress into a more severe form. Hence, the use of GLP1-RA might prevent Covid-19 progression by controlling gut microbiota dysbiosis which was precipitated by diabetes mellitus and/or obesity.[51,52]

We are aware of some limitations in our study. First, our study is only based from observational studies which are not free from the potential influence of confounding factors. Second, most of the included studies do not include information regarding the dosage and the duration of GLP-1RA use, therefore we are unable to analyze and provide drug dose and duration recommendation. Finally, the result from our analysis was dominantly affected by 2 studies which have large weight during the meta-analysis calculation, probably because of large sample sizes, therefore the results from our study should be interpreted with caution.

5. Conclusion

Our meta-analysis indicates that pre-admission use of GLP-1RA have an association with favorable mortality outcomes of Covid-19 in patients with diabetes mellitus. This study suggests that GLP-1RA have the potency to be the drug of choice for the management of type 2 diabetes mellitus patients during COVID-19 pandemic to improve patients' outcome, especially those who have cardiovascular risk factors. Importantly, we believe further randomized clinical trial studies are worthwhile to confirm our study. Finally, GLP-1RA should be put into consideration as an important agent in COVID-19 treatment plan.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

Data analyzed in this study were a re-analysis of existing data, which are openly available at locations cited in the reference section.

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